# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>2139-32PCT | **FOR FURTHER ACTION** | See item 4 below |
| International application No.<br>PCT/CA2004/001794 | International filing date *(day/month/year)*<br>22 October 2004 (22.10.2004) | Priority date *(day/month/year)*<br>24 October 2003 (24.10.2003) |
| International Patent Classification (8th edition unless older edition indicated)<br>See relevant information in Form PCT/ISA/237 | | |
| Applicant<br>NATIONAL RESEARCH COUNCIL OF CANADA# | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☒ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☒ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

| | |
|---|---|
| | Date of issuance of this report<br>24 April 2006 (24.04.2006) |
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br>Facsimile No. +41 22 740 14 35 | Authorized officer<br>Athina Nickitas-Etienne<br>Telephone No. +41 22 338 89 95 |

Form PCT/IB/373 (January 2004)

CORRECTED VERSION
20 April 2005

**PATENT COOPERATION TREATY**



From the INTERNATIONAL SEARCHING AUTHORITY

To:
OGILVY RENAULT
1600 - 1981 McGill College Avenue
MONTREAL, Quebec
Canada, H3A 2Y3

06.05.05

**PCT**

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

**(PCT Rule 43*bis*.1)**

| Date of mailing *(date/month/year)* | 24 February 2005 (24-02-2005) |
|---|---|

| Applicant's or agent's file reference | **FOR FURTHER ACTION** See paragraph 2 below |
|---|---|
| 2319-32PCT | |

| International application no | International filing date *(date/month/year)* | Priority date *(date/month/year)* |
|---|---|---|
| PCT/CA2004/001794 | 22 October 2004 (22-10-2004) | 24 October 2003 (24-10-2003) |

International Patent Classification (IPC) or both national classification and IPC

C12N 7/01; A61K 48/00; C12N 15/861; C12N 5/10

Applicant NATIONAL RESEARCH COUNCIL OF CANADA

1. This opinion contains indications relating to the following items :

| | | |
|---|---|---|
| [X] | Box No. I | Basis of the opinion |
| [X] | Box No. II | Priority |
| [ ] | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| [X] | Box No. IV | Lack of unity of invention |
| [X] | Box No. V | Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| [ ] | Box No. VI | Certain documents cited |
| [ ] | Box No. VII | Certain defects in the international application |
| [X] | Box No. VIII | Certain observations on the international application |

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| *Commissioner of Patents*<br>*Canadian Patent Office*<br>*Box PCT, Ottawa/Gatineau K1A 0C9* | Nancy L. Trus (819) 953-3355 |
| Facsimile No. (819) 953-9538 | |

Form PCT/ISA/237 (cover sheet) (January 2004)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CA2004/001794

**Box No. I Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language which it was filed, unless otherwise indicated under this item.

[ ] This opinion has been established on the basis of a translation from the original language into the following language __ , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :

a. type of material

[X] a sequence listing

[ ] table(s) related to the sequence listing

b. format of material

[X] in written format

[X] in computer readable from

c. time of filing/furnishing

[X] contained in the international application as filed.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority for the purposes of search.

3. [X] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
**PCT/CA2004/001794**

**Box No. II Priority**

1 [X] The following document has not yet been furnished :

[X] copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

[ ] translation of the earlier application whose priority has been claimed (rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2 [ ] This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purpose of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary :

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CA2004/001794

**Box No. IV** **Lack of unity of invention**

1 [ ] In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has :

[ ] paid additional fees

[ ] paid additional fees under protest

[ ] not paid additional fees

2 [ ] This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3 This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

[X] complied with

[ ] not complied with for the following reasons :

4 Consequently, this opinion has been established in respect of the following parts of the international application :

[X] all parts

[ ] the parts relating to claims Nos. ____

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No. PCT/CA2004/001794

**Box No. V reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 10, 11, 14, 15, 23, 24 | YES |
| | Claims | 1-9, 12, 13, 16-22, 25-30, 32, 33 | NO |
| Inventive step (IS) | Claims | 10, 11, 14, 15, 23, 24 | YES |
| | Claims | 1-9, 12, 13, 16-22, 25-33 | NO |
| Industrial applicability (IA) | Claims | 1-33 | YES |
| | Claims | | NO |

2. Citations and explanations :

D1 BARNETT, B.G., et. al. "Targeted adenoviral vectors", BIOCHIMICA ET BIOPHYSICA ACTA, ELSEVIER, AMSTERDAM, NL. 3 May 2002 (3.05.2002) vol. 1575, no. (1-3), pages 1-14 PMID 12020813. In particular see pages 7-9.

D2 KRASNKH, V., et. al. "Genetic Targeting of an Adenovirus Vector via Replacement of the Fiber Protein with the Phage T4 Fibritin" JOURNAL OF VIROLOGY, AMERICAN SOCIETY FOR MICROBIOLOGY, May 2001, vol. 75 pages 4176-4183

D3 EINFELD, D.A., et. al. "Construction of a pseudoreceptor that mediates transduction by adenoviruses expressing a ligand in fiber or penton base" JOURNAL OF VIROLOGY, AMERICAN SOCIETY FOR MICROBIOLOGY, November 1999, vol. 73, no. 11, pages 9130-9136 PMID 10516019

D4 NICLIN, S.T., et. al. "Ablating Adenovirus Type 5 Fiber-CAR Binding HI Loop Insertion of the SIGYPLP Peptide Generate an Endothelial Cell-Selective Adenovirus" MOLECULAR THERAPY, THE AMERICAN SOCIETY OF GENE THERAPY, December 2001, vol. 4, no. 6, pages 534-542 PMID 11735337

D5 CA 2,234,073 A1 (HOUSTON, M.E. Jr., et. al.; Pence Inc.) 10 April 1997 (10.04.1997)

D6 CA 2,190,494 A1 (HODGES, R.S., et. al.; Pence Inc.) 23 November 1995 (23.11.1995)

Novelty and Inventive Step - Articles 33(2) and 33(3) PCT

Claims 1-9, 12, 13, 16-22 and 25-33 lack novelty and are anticipated by D1, D2, D3 and D4 and therefore fail to meet the requirements of Article 33(2) of the PCT.

D1 provides a review of the prior art developments in the field of targeted adenovirus (Ad) vectors. Various strategies for ablation of native specificity and retargeting are discussed. Specific reference is made on page 7 to incorporation of novel targeting ligands into the Ad vectors. On page 8 genetic manipulation of Ad to replace the fiber structure to ablate native specificity and retarget the vectors is described. Reference is made on page 9 to strategies for preparation of specific cell lines necessary for the propagation of targeted vectors.

D2 describes the generation of an Ad vector lacking wild-type fibers but instead containing a fiber chimera consisting of the tail domain and two pseudorepeats of the N-terminus of the Ad5 fiber genetically fused to the trimeric bacteriophage T4 fibritin protein, with its N-terminus deleted. A 6-histidine tag was connected to the C-terminus of the fibritin protein via a short peptide linker. The 6 His tag functioned as a targeting motif. The chimeric vectors were capable of CAR-independent infection of target cells expressing an artificial receptor in the form of a single chain antibody specific for 6 His.

D3 describes an alternative receptor, or pseudoreceptor, system that employs a hemagglutinin (HA) epitope incorporated into the Ad capsid. An anti-HA single chain antibody expressed on target cells functions as the complementary receptor for propagation of the viruses which have had the native CAR receptor system ablated.

D4 describes the development of a genetically modified Ad with altered tropism. By inserting endothelial cell binding peptides into the HI loop of the fiber, the Ad viruses demonstrated selective tropism for endothelial cells. Point mutations were used to ablate the CAR-dependent specificity.

(Continued on Supplemental Box)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/CA2004/001794

**Box No. VIII** **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

**A. Claim Defects**

Claims 1 to 33 do not meet the requirements of Article 6 of the PCT. Applicant describes the preparation of modified adenovirus vectors having either the E-coil or K-coil peptide inserted into the fiber knob and having the native CAR-dependent specificity ablated. Applicant also describes the preparation of permissive cells expressing the complementary peptide (K-coil or E-coil respectively) for use in the propagation of the modified Ad vectors.

Applicant does not provide support for the preparation of other than Adenovirus type vectors. Nor does applicant provide support for the insertion of any "non-native peptides" other than K-coil and E-coil.

Claims 1, 12, 13 and 21 fail to include the technical features required to fully define the invention as required under Rule 6.3(a) of the PCT. As specified above, the virus and permissive cell must be restricted to those expressing E-coil or K-coil as binding moieties and receptors in keeping with the scope of the disclosure.

**Supplemental Box**

**In case the space in any of the preceding boxes is not sufficient.**
Continuation of :

Box V:

Modified viruses with ablated natural receptors containing non-native peptides which alter tropism are therefore well known in the art, as are cells containing them and permissive cells which have been developed specifically for the propagation of the modified viruses.

Claims 10, 11, 14, 15, 23 and 24 directed to modified adenoviruses having either the E-coil or K-coil peptide inserted and permissive cells having the complementary coil sequence expressed as a surface receptor, appear to meet the requirements of Article 33(2) of the PCT. The subject matter of these claims would also appear to contain an inventive step and therefore meet the requirements of Article 33(3) of the PCT.

Industrial Applicability - Article 33(4) PCT

Claims 1 to 33 appear to define subject matter that has industrial applicability under Article 33(4) of the PCT, based on the use of the E-coil/K-coil system to prepare modified viruses with altered tropism and permissive host cell lines for the propagation of the altered viruses.